



Armato, S. G., Blyth, K. G., Keating, J. J., Katz, S., Tsim, S., Coolen, J., Gudmundsson, E., Opitz, I. and Nowak, A. K. (2016) Imaging in pleural mesothelioma: a review of the 13th International Conference of the International Mesothelioma Interest Group. *Lung Cancer*, 101, pp. 48-58.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/131292/>

Deposited on: 14 December 2017

Enlighten – Research publications by members of the University of Glasgow_
<http://eprints.gla.ac.uk>

Imaging in Pleural Mesothelioma: A Review of the 13th International Conference of the International Mesothelioma Interest Group

Samuel G. Armato III, Ph.D.¹

Kevin G. Blyth, MBChB, FRCP, M.D.²

Jane J. Keating, M.D.^{3,4}

Sharyn Katz, M.D.⁵

Selina Tsim²

Johan Coolen, M.D.⁶

Eyjolfur Gudmundsson¹

Isabelle Opitz, M.D.⁷

Anna K. Nowak, MBBS FRACP Ph.D.⁸

¹Department of Radiology, The University of Chicago, Chicago, Illinois, USA

²Department of Respiratory Medicine, Queen Elizabeth University Hospital, Glasgow, UK and
Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK

³Department of Surgery, University of Pennsylvania School of Medicine and Philadelphia
Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA

⁴Center for Precision Surgery, Abramson Cancer Center, University of Pennsylvania Pearlman
School of Medicine, Philadelphia, Pennsylvania, USA

⁵Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

⁶Department of Radiology, University Hospitals Leuven, Belgium

⁷Division of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland

⁸School of Medicine and Pharmacology, University of Western Australia, Perth, Western
Australia and Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth,
Western Australia, Australia

Corresponding Author:

Samuel G. Armato III, Ph.D.
Department of Radiology
The University of Chicago
5841 South Maryland Ave., MC 2026
Chicago, IL, USA 60637
s-armato@uchicago.edu

Key words: mesothelioma, near-infrared imaging, indocyanine green, delayed phase enhancement MRI, early contrast-enhancement MRI, perfusion MRI, dynamic contrast-enhanced CT, tumor response assessment, tumor volume, tumor weight, modified RECIST

ABSTRACT

Imaging plays an important role in the detection, diagnosis, staging, response assessment, and surveillance of malignant pleural mesothelioma. The etiology, biology, and growth pattern of mesothelioma present unique challenges for each modality used to capture various aspects of this disease. Clinical implementation of imaging techniques and information derived from images continue to evolve based on active research in this field worldwide. This paper summarizes the imaging-based research presented orally at the 2016 International Conference of the International Mesothelioma Interest Group (iMig) in Birmingham, United Kingdom, held May 1-4, 2016. Presented topics included intraoperative near-infrared imaging of mesothelioma to aid the assessment of resection completeness, an evaluation of tumor enhancement improvement with increased time delay between contrast injection and image acquisition in standard clinical magnetic resonance imaging (MRI) scans, the potential of early contrast enhancement analysis to provide MRI with a role in mesothelioma detection, the differentiation of short- and long-term survivors based on MRI tumor volume and histogram analysis, the response-assessment potential of hemodynamic parameters derived from dynamic contrast-enhanced computed tomography (DCE-CT) scans, the correlation of CT-based tumor volume with the post-surgical tumor specimen weight, and consideration of the need to update the mesothelioma tumor response assessment paradigm.

1. Introduction

The International Mesothelioma Interest Group (iMig) (www.imig.org) holds a biennial conference to which advances in imaging research and clinical applications of imaging technologies have made key contributions [1-4]. Researchers, clinicians, and radiologists continue to seek ways to expand the capabilities of imaging with the intent of extracting as much anatomic or physiologic information from mesothelioma patients as possible and to apply imaging technologies most appropriately to patient management in both routine practice and clinical trials research. This paper summarizes research presented in the “Imaging and Endpoint Evaluation” session of the 2016 International Conference of the International Mesothelioma Interest Group in Birmingham, United Kingdom, May 2016.

Key clinical goals of imaging in malignant pleural mesothelioma are early detection of disease, optimising sensitivity and specificity for anatomic involvement of unresectable planes to identify patients who are suitable for surgical resection, improving prognostication, and assessing response to treatment as a surrogate for therapeutic benefit. The imaging reported in the context of mesothelioma typically includes computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans; these scans may be acquired during initial tumor diagnosis and staging, treatment response assessment, or patient surveillance, depending on the clinical question being asked. Optical imaging, using electromagnetic radiation in (or near) the visible light region of the spectrum, has been an active area of research for a wide range of medical applications [5] and is now being applied in the intraoperative setting for mesothelioma. Initial results indicate the potential for optical imaging to aid surgeons in their attempt to achieve a macroscopic complete resection.

The advancement of MRI for the benefit of mesothelioma patients continues to attract the attention of clinical investigators. Tumor contrast enhancement in MRI has long provided information about tumor vascularity, but new evidence suggests that the clinically conventional time delay between contrast injection and initiation of image acquisition might be too short for optimal assessment of mesothelioma. Juxtaposed with the potential need for longer delay times in standard MRI is a perfusion-based MRI technique designed to capture *early* contrast-enhancement features of the pleura that might be characteristic of early-stage mesothelioma, thus enabling a possible tumor detection role for MRI in this setting. MRI also offers functional imaging capabilities through diffusion-weighted imaging (DWI), which is being used to compute tumor volume and parameters of the tumor pixel-value histogram in an attempt to differentiate between patients with long- and short-term overall survival.

Imaging of tumor perfusion with computed tomography (CT) has become routine for some tumors; however, dynamic contrast-enhanced computed tomography (DCE-CT) has only recently been applied to mesothelioma [3]. Investigation of this imaging technique continues with the computation of hemodynamic parameters designed to capture physiologic changes in the tumor that are not necessarily reflected in tumor thickness change. The ultimate goal of this approach is an earlier assessment of pharmacodynamic endpoints and tumor response.

The potential role of image-based mesothelioma tumor volume in staging [6], the impact of volume on tumor response assessment [7-10], the correlation between tumor volume and patient survival [7-9,11], and the computerized extraction of mesothelioma tumor volume from CT scans [12] have all been the subject of recent investigation. Mesothelioma, however, presents a unique challenge for image-based tumor volumetrics; before mesothelioma tumor volume can be adopted for clinical application, it is essential to understand the correlation

between tumor volume derived from images and the actual, physical tumor bulk that the images represent. Although physical tumor weight and volume have been shown to relate to patient survival [13], the reliability of extrapolating physical tumor volume from imaging has been questioned in previous studies [14]. Ongoing work in this regard continues to demonstrate only moderate correlation between image-based mesothelioma tumor volume and both the physical weight of the resected tumor and the pathologic T stage.

Objective radiologic response rate is the key efficacy endpoint in early development of new therapies. In phase II trials, response rate is often the primary study endpoint, and even in randomised phase III studies, response rate may be used as a correlative measure of efficacy. The morphology and growth characteristics of mesothelioma, however, differ from many other solid tumors in that the disease often forms a rind around the pleural cavity, with a sheet-like rather than spherical growth pattern. The RECIST (Response Evaluation Criteria in Solid Tumors) guidelines [15] used unidimensional measurements, which were ostensibly better suited for measurement of mesothelioma rind thickness; however, RECIST required measurement of a tumor's longest diameter, and the underlying assumption was of a spherical growth pattern. The poor suitability of RECIST for measurement of mesothelioma and discrepancies between patient response based on RECIST and the earlier World Health Organization (WHO) guidelines [16] were soon revealed [17-18]. Modified RECIST for mesothelioma [19] was developed to address this deficiency. Discrepancies in the practical implementation of modified RECIST, however, have led to confusion and inconsistent approaches to tumor measurement and response assessment. This concern, along with the update to RECIST that was provided by RECIST 1.1 [20], indicate that a revision to modified RECIST is needed.

2. Imaging with indocyanine green for intraoperative detection of residual disease

A subset of patients with epithelioid malignant mesothelioma limited to the hemithorax may benefit from an approach that includes surgery involving extrapleural pneumonectomy or a lung-preserving operation such as pleurectomy/decortication [21]. Regardless of the approach, the goal of surgery is macroscopic complete resection. Despite aggressive multimodality therapy for “resectable” mesothelioma, prognosis remains poor, potentially in part due to residual disease. At the conclusion of surgery, it can be challenging to discriminate residual disease from scar and normal tissue [22]. Keating and colleagues used near-infrared (NIR) molecular imaging using indocyanine green (ICG) for the intraoperative localization of tumors, lymph nodes, and metastases [23-25] and, more specifically, for the evaluation of margins following mediastinal tumor resection [26]. ICG is a non-targeted, near-infrared optical contrast agent that localizes to tumors through the enhanced permeability and retention effect. This group investigated NIR intraoperative molecular imaging with ICG for the detection of mesothelioma tumor deposits to assess for resection completeness.

Eight patients with biopsy-proven epithelial malignant pleural mesothelioma were enrolled in a pilot clinical trial. All patients underwent 5 mg/kg of intravenous ICG injection 24 hours prior to surgery. The following day, a NIR imaging device was used to detect tumor fluorescence intraoperatively. After what was believed to be complete tumor excision, the wound bed was reimaged for residual fluorescence indicative of retained tumor. When residual fluorescence was detected, additional tissue was resected, if feasible. Specimens were sent for pathologic correlation.

All patients underwent ICG injection with no evidence of drug toxicity. Intraoperative NIR fluorescence localized to mesothelioma in all cases. Following tumor excision,

fluorescence was confirmed ex vivo (Figure 1). The mean *in vivo* NIR tumor-to-background ratio was 3.2 (IQR 2.9-3.4). After what was thought to be complete tumor excision, residual disease was discovered upon wound-bed imaging in all eight patients. The number of additional resected specimens following wound-bed imaging ranged from one to four (mean 1.8). Disease was typically discovered in difficult-to-reach places, including the costophrenic sulcus and directly beneath or adjacent to the thoracotomy incision. The mean NIR tumor-to-background ratio of the resected residual tumor deposits was 2.8 (IQR 2.6-3.1); these resected specimens ranged in size from 0.3 mm to 2.2 cm (mean 0.9 cm). In all cases, the additionally resected fluorescent tissue was confirmed as malignant mesothelioma on pathology.

In conclusion, NIR intraoperative molecular imaging using ICG localizes to malignant pleural mesothelioma and aids in detection of residual disease for improved resection. A larger clinical trial is needed to investigate the impact of NIR intraoperative imaging on patient survival.

3. Utility of delayed phase enhancement MRI

Although modern cross-sectional imaging has high spatial resolution, limitations in tissue contrast remain a challenge for staging of malignant pleural mesothelioma. This limitation is a particular challenge on CT, where mesothelioma has a similar tissue attenuation to adjacent structures including chest wall musculature, diaphragm and pericardium, and complex pleural effusions [27,28]. Unfortunately, on conventional imaging protocols, mesothelioma often does not enhance sufficiently to allow for consistent, accurate pre-operative staging. Since MRI has superior tissue contrast, MRI is sometimes employed to further characterize mesothelioma cases suspicious for local invasion on CT [27]. Although MRI does have superior tissue contrast,

subtle local invasion can still be a challenge to detect with imaging. Limitations in imaging are partially responsible for the significant upstaging of disease that occurs in patients with mesothelioma who undergo pleurectomy; in a study by Rusch *et al.*, for example, as many as 80% of patients with stage 1 and 2 disease and 23% of patients with stage 3 disease were upstaged post-operatively [21].

To determine whether tumor enhancement is optimal at the conventional imaging phase post intravenous contrast injection, Katz and colleagues conducted a retrospective study of patients with mesothelioma undergoing MRI for pre-operative staging. Since these examinations included pre-contrast imaging and multiple acquisitions following injection of intravenous gadolinium, a time-enhancement curve for each patient could be constructed. MRI exams for a total of 10 patients were analyzed; each scan demonstrated tumor with a thickness measurement of at least 5 mm, and all analyzed series had been acquired with fixed image-acquisition parameters. Regions of interest were obtained from each phase of enhancement, and time-enhancement curves were generated using maximal signal intensities (normalized to background) at each time delay. These analyses revealed that the mesothelioma tumor enhancement at the conventional phase delay (40-60 sec) did not represent the maximal possible tumor enhancement, which occurred at a later time point for all 10 patients (Figure 2).

To estimate an optimal time delay for mesothelioma enhancement, the MRI enhancement data from these patients were employed to create best-fit models, which then were used to determine predicted maximum values. Based on this technique, the peak tumor enhancement was estimated to occur at 280 sec following IV contrast administration. At a time delay of 280 sec, 70% and 60% of patients are projected to have reached >85% and >90%, respectively, of the peak projected signal intensity.

These data strongly suggest that the optimal mesothelioma contrast enhancement on MRI occurs at a time delay longer than is typically employed in routine clinical imaging. This finding is important since improved tumor enhancement may allow for increased accuracy in staging and therapy response assessment through improved tissue contrast. Since the kinetics of intravenous contrast administration on CT is similar to MRI, it is highly likely that conventional CT chest imaging also could achieve improved tumor enhancement at a greater time delay than typically employed (40-60 sec). The impact of delayed phase enhancement on radiologic mesothelioma staging accuracy and therapy response assessment warrants further study, since accurate staging is critical to providing patients with the best opportunity for treatment success.

4. Optimization of early contrast-enhancement MRI

Radiologic detection of pleural malignancy is difficult, because pleural thickening may be minimal or absent, particularly in early-stage malignant pleural mesothelioma. Moreover, pleural tumours are frequently distributed heterogeneously over a large area and interspersed with regions of benign or normal pleura. These challenges are reflected in routine diagnostic CT scans, with two recent studies reporting CT sensitivities for pleural malignancy of 68% and 57% [29-30]. In a pilot study, Tsim and colleagues sought to develop a novel perfusion-based MRI biomarker for pleural malignancy that utilises the high spatial resolution provided by MRI; this technique was intended to target typical early features of the pleural tumour micro-environment, including neovascularisation and increases in constituent blood vessel density [31-32].

Twenty-four patients with suspected mesothelioma prospectively underwent contrast-enhanced CT, MRI, and subsequent diagnostic thoracoscopy. The MRI protocol was developed with the first six patients; the subsequent 18 patients had complete contrast-enhanced MRI scans,

which consisted of T1-weighted, 3D-spoiled-gradient-echo sequences acquired at baseline, 40 seconds, 80 seconds, and 4.5, 9, and 13.5 minutes after contrast injection. The mean signal intensity of representative parietal pleura was measured in 15 regions of interest (ROIs) (Figure 3(a) and (b)). Early contrast enhancement (ECE) was defined objectively by an early (≤ 4.5 minutes) peak in mean signal intensity. Patient images were classified as malignant if at least one ROI demonstrated ECE (Figure 3(c) and (d)). Signal intensity gradient was calculated (1) within individual ROIs and (2) per patient as the mean across all ROIs. Diagnostic performance and inter-observer agreement for ECE were evaluated. Mean signal intensity gradient for each patient was correlated with microvessel density measured in paraffin-embedded thoracoscopic pleural biopsies from representative anatomic regions and stained with CD34 and Factor VIII. To assess the contribution of interspersed benign disease to the diagnostic performance of ECE, receiver operating characteristic (ROC) curves were plotted based on the signal intensity gradient within all ROIs and then based on the signal intensity gradient only from ROIs demonstrating ECE in patients with pleural malignancy versus benign disease (Figure 3 (e) and (f)).

Eighteen of the 24 patients (mean age 73 ± 8 years) had a history of asbestos exposure, and twelve of these patients had maximum pleural thickening ≤ 10 mm. The diagnostic performance and reproducibility of ECE were as follows: sensitivity 91%, specificity 86%, positive predictive value 91%, negative predictive value 85%, and inter-observer agreement 0.766. A moderate correlation was obtained between mean signal intensity gradient and microvessel density measured using both CD34 and Factor VIII ($r=0.63$, $p=0.044$ and $r=0.72$, $p=0.016$, respectively).

It is interesting to note the concordance in peak contrast-enhancement time points reported in this study and the study by Katz in the previous section. 65% (66/101) of the malignant ROIs defined in this study peaked at 4.5 minutes, consistent with the 280-second peak

reported independently by Katz. Future studies will allow greater understanding of how these observations relate to each other and how they can best applied. This work will also hopefully lead to common terminology, since the use of “early contrast enhancement” and “delayed phase enhancement” for potentially similar contrast behaviour is likely to lead to confusion.

In this pilot study ECE appeared to be an accurate and reproducible, perfusion-based biomarker of pleural malignancy. A larger study is required to reliably define the performance of ECE relative to existing approaches, including CT- and MRI-based tumor morphology. Excluding ECE-negative ROIs improved the discriminant performance of the ROI-based signal-intensity gradient, probably because these areas represent interspersed benign pleural disease in patients with low-volume pleural malignancy (confirmed thoracoscopically in this study). ECE assessment can be performed in patients with minimal pleural thickening, suggesting a potential role in the detection of early-stage mesothelioma or low-volume metastatic pleural metastases.

5. Histogram analysis of DW-MRI during early chemotherapy to predict outcome

Patients with unresectable malignant pleural mesothelioma are most commonly treated with palliative chemotherapy, while treatment efficacy is radiologically monitored using modified RECIST to evaluate change in tumor thickness. Anatomy-based assessments of response have limitations, however, which is one reason why prediction of survival is often difficult [33]. Even multiparametric MR imaging parameters can be insufficient for differentiating long- and short-term surviving patients, probably due to the large heterogeneity of disease phenotypes, which strongly influences response to therapy and disease appearance on imaging. In this study Coolen and colleagues examined the value of diffusion-weighted MR

imaging (DWI) using tumor volume and four first-order histogram-based parameters (mean, standard deviation, skewness, and kurtosis) to assess treatment outcome.

Fifteen consecutive patients with inoperable mesothelioma undergoing systemic palliative chemotherapy (cisplatin-pemetrexed) were included in the study. Anatomic and functional sequences (including DWI acquired using different diffusion sensitivities with six b-values up to 1000 mm²/s, from which the apparent diffusion coefficient maps can be calculated [34]) were performed on a 3T MRI scanner according to a previously established protocol [35] at baseline and again after one month, just before the second chemotherapy session. Histograms of apparent diffusion coefficient (ADC) values were constructed for each patient based on the ADC_{avg} (calculated from all six b-values) of each pixel within the tumor and the ADC_{low} (calculated from the first three b-values: 0, 50, and 100 mm²/s) of each pixel within the tumor. Differences in volume and the first-order histogram parameters between patients with long-term and short-term progression-free survival (PFS, cut-off: 170 days) and overall survival (OS, cut-off: 440 days) were calculated, and Mann-Whitney *U* tests were used to evaluate statistical significance.

When using baseline scan parameters to differentiate between patients with long- and short-term OS, the kurtosis of the ADC_{low} histogram and the skewness of the ADC_{low} histogram were significantly different ($p=0.004$ and 0.006 , respectively) with thresholds of 8.25 and 2.25, respectively (higher values indicated shorter OS). Also, higher baseline tumor volumes were indicative of shorter OS ($p=0.009$, threshold 772 ml). Figure 4 illustrates a case for which the parameters predict a good prognosis despite inoperable stage IV disease.

Similar findings were observed at the follow-up time point, for which the mean, kurtosis, and skewness of the ADC_{low} histogram were significantly different between long- and short-term

OS patients (p-values 0.004, 0.02, and 0.014, respectively). Lower ADC_{low} mean (threshold: $3.25 \times 10^{-7} \text{ mm}^2/\text{s}$) and higher ADC_{low} kurtosis (threshold: 10) and skewness (threshold: 2.3) were indicative of shorter OS. Higher follow-up tumor volumes were indicative of shorter OS (p=0.009, threshold 386 ml). These results were improved relative to tumor ADC values alone [3]. As expected, the results for differentiating between long- and short-term PFS were less encouraging, with only kurtosis of the baseline ADC_{avg} histogram and mean of the follow-up ADC_{low} histogram nearing significance (p=0.054 and 0.07, respectively); lower values of both parameters were predictive of shorter PFS.

First-order histogram analysis of ADC parameters during early palliative chemotherapy of inoperable mesothelioma patients can differentiate between patients with long- and short-term OS, although PFS separation is less accurate. Histogram analysis demonstrates tumor heterogeneity and is the foundation for DWI as a biomarker [36-37]. Moreover, these findings suggest that DWI could be a useful tool for personalized care in mesothelioma patients; when a second-line option becomes clinically available (currently a highly unmet need), this type of therapy response evaluation will become especially crucial. These preliminary data, however, require confirmation in a larger patient cohort, preferably with multicenter participation.

6. Dynamic contrast-enhanced CT to assess tumor response

Clinical assessment of tumor response to treatment in malignant pleural mesothelioma patients currently relies on linear measurements of tumor thickness obtained according to the modified RECIST protocol [19]. Hemodynamic parameters derived from dynamic contrast-enhanced computed tomography (DCE-CT) scans have been shown to be representative of physiologic changes in tumor tissue not necessarily reflected by changes in tumor thickness [38].

Few investigations have been made into the use of such hemodynamic parameters for the assessment of tumor response in mesothelioma patients. A study by Gudmundsson and colleagues evaluated the utility of DCE-CT in the assessment of mesothelioma tumor response.

The standard CT imaging protocol for mesothelioma was modified to include a DCE-CT component, during which a 55-mm axial extent of thoracic anatomy demonstrating notable tumor burden was imaged at specific time points following the injection of contrast media. The DCE-CT image-acquisition protocol included two dynamic phases, one during the first minute following contrast injection and another starting at approximately 115 seconds after the initial injection of contrast, following the acquisition of a standard CT scan of the full chest. The patient cohort consisted of 16 non-consecutive mesothelioma patients, of whom eight were on treatment (including Vorinostat, Pemetrexed, cisplatin or carboplatin/Pemetrexed, cisplatin/Pemetrexed/CBP501, and GDC-0980) and eight were on observation. After providing written informed consent, each patient underwent two clinically indicated CT scans, separated by approximately two months, that were augmented with the DCE-CT scan components.

To capture tumor burden in each standard CT scan, modified RECIST measurements [19] were obtained manually by a research radiologist, and CT-based tumor volume measurements were obtained using a semi-automated in-house method [7]. To define a region of interest for the computation of hemodynamic parameters, visible tumor (which might comprise more than one focus of disease) was manually contoured on the images from a single time point of the dynamic phases of each scan; these contours were automatically propagated across all time points within the scan using a deformable image registration technique [39]. The hemodynamic parameters of perfusion, peak CT value enhancement, blood volume, and time to peak enhancement [40-41] were calculated from the average of the contrast uptake curves obtained

from individual pixels within the tumor regions. Changes in these parameters were calculated between the two DCE-CT scans acquired from each patient, and the means of the change in individual parameters were compared between the on-treatment and on-observation cohorts.

Although changes in hemodynamic parameters were not significantly different between the two patient cohorts for any of the measured parameters, patients on treatment demonstrated a mean relative decrease in blood volume and perfusion (-14.2% and -17.2%, respectively) compared with a mean relative increase in these parameters (+8.8% and +27.0%, respectively) for patients on observation. Figure 5 shows the blood-volume map from an on-therapy mesothelioma patient that exhibits a mean decrease in blood volume of 25.6% between the two scans following two cycles of chemotherapy, whereas summed tumor thickness as measured by modified RECIST for this patient showed an increase of 12.8% between scans. No statistically significant correlation was found across all patients between relative changes in hemodynamic parameters and changes in tumor size, either by modified RECIST or tumor volume.

Observed differences in hemodynamic parameter changes between patients on treatment and patients on observation suggest that DCE-CT could be a useful imaging modality for the assessment of pharmacodynamic endpoints in mesothelioma. The clinical relevance of these trends should be investigated through future studies with larger numbers of patients and focused therapeutic regimens.

7. Correlation of CT-based tumor volume and resected tumor weight

Tumor volume has been reported to be a valuable prognosticator for survival in patients with malignant pleural mesothelioma [6-7, 11, 42]. Opitz and colleagues sought to assess the

precision of preoperative CT-based tumor volume in terms of correlation with the actual weight of tumor resected during macroscopic complete resection.

Between October 2012 and March 2016 the weight of resected tumor specimens was measured in 28 patients undergoing (extended) pleurectomy/decortication ((e)P/D). Median patient age at the time of surgery was 66 years (range 41–77 years). Eighteen patients (64%) had right-sided mesothelioma, and mesothelioma showed an epithelioid histology in 26 patients (93%). Three patients (11%) showed pathologic T (pT) stage 1, 8 (28%) patients were pT stage 2, 14 (50%) patients were pT stage 3, and 3 (11%) patients were pT stage 4. Median time between the pre-operative CT scan and surgery was 17 days (range 1-48 days).

Tumor volume in the pre-operative contrast-enhanced CT scan (n=19) or non-contrast-enhanced CT component of the PET-CT scan (n=9) of all 28 patients was measured by an experienced radiologist using a commercially available semi-automated method as described previously [10]. On the CT component of the PET-CT scan, the initially semi-automated segmented tumor volume was modified manually in correlation with the PET images, which were scrolled simultaneously in a separate window; included in the tumor volume was soft tissue that corresponded with regions of fluorodeoxyglucose (FDG) activity and soft tissue that did not show FDG activity but that could be identified clearly as mesothelioma because of its nodular morphology. Physical tumor volume was measured through a water-displacement method; the resected tumor specimen was submerged in a 1-liter graduated cylinder filled with 500 ml of physiologic salt solution, and the resulting increase in volume was recorded as tumor volume. Relations between tumor weight, tumor volume at surgery, CT-volume, cT stage and pT stage were analyzed using Spearman rank correlation.

The median tumor volume assessed by CT was 53 ml (range 2-709 ml), and the median post-surgical tumor weight was 398 g (range 95-783 g). The analysis revealed a moderate correlation between CT-based tumor volume and tumor weight (correlation coefficient 0.47, $p=0.01$) (Figure 6). CT tumor volume and physical post-surgical tumor volume demonstrated moderate correlation (correlation coefficient 0.55, $p=0.02$), consistent with other studies [14]. No significant correlation was observed between clinical T (cT) stage and tumor weight (correlation coefficient 0.31, $p=0.1$). There was a weak correlation of CT tumor volume with pT stage (correlation coefficient 0.38, $p=0.04$) and a moderate correlation of tumor weight with pT stage (correlation coefficient 0.51, $p=0.006$).

The correlation between preoperatively assessed CT-based tumor volume and actual resected tumor weight was only moderate, but weight included more structures than tumor alone, such as pericardium and diaphragm. The physical volume of the resected tumor specimen also was moderately correlated with the CT-measured volume. Correlation between CT tumor volume and pT stage was only moderate; however, CT tumor volume is a better parameter for prediction of actual tumor weight in comparison to cT (both assessed by experienced radiologist). The independent effect of the different variables on overall survival could not be assessed in the present analyses and will be further investigated.

8. Towards modified RECIST 1.1

Modified RECIST [19] substantively altered the manner in which unidimensional measurements were acquired from the CT scans of malignant pleural mesothelioma patients. The measurement of longest tumor diameter specified by RECIST [15] was replaced, in modified RECIST, by tumor thickness measurements, and the up-to-ten target lesions of

RECIST was replaced by six measurement sites within the tumor. Notably, while altering the vector in which the tumor was measured, modified RECIST did not attempt to alter the RECIST criteria for measurability or response. Despite the underlying assumption that all other aspects of RECIST were to remain unaltered by the application of modified RECIST to mesothelioma, misinterpretations have evolved in its clinical implementation. Furthermore, modified RECIST was conceived of and published as research to validate this new measurement paradigm and solve a key problem in the mesothelioma clinical research community; it was not intended to comprehensively describe a set of response criteria suitable for clinical trial implementation. The authors specifically noted that “further evaluation of these modified criteria should be performed before they can be incorporated routinely into future clinical trials” [19]; nevertheless, modified RECIST almost immediately became the standard for mesothelioma tumor response assessment.

Since modified RECIST was published, a number of gaps in application have become apparent, the relevance of some aspects of RECIST to mesothelioma has been questioned, and unaddressed issues have been identified (Figure 7). Subsequent reports have sought to define the logistics of practical implementation of modified RECIST [43] or record inter-observer variability [44-45], but misinterpretations remain. Furthermore, RECIST 1.1 [20] updated several aspects of RECIST in 2009, and an analogous, logically consistent revision of modified RECIST (“modified RECIST 1.1”) is warranted.

Modified RECIST 1.1 guidelines will need to address several important issues: (1) the definition of “minimum measurable disease” in mesothelioma, (2) the relevance of “target lesion” for a spatially distributed tumor such as mesothelioma, (3) the selection of measurement sites, (4) the role of non-pleural disease, (5) the impact of non-measurable pleural disease, and

(6) the definition of progressive disease. The response classification criteria (the actual numeric values) that separate “partial response” from “stable disease” from “progressive disease” in mesothelioma are under investigation [46-47] but would require clinical trial validation prior to the recommendation of any alteration to the now-standard 30% decrease and 20% increase specified by RECIST; therefore, modified RECIST 1.1 will not address tumor response criteria.

A recent study [48] reported a clinically acceptable level of mesothelioma tumor thickness measurement variability for thicknesses in the range 5.0-7.5 mm; thus, modified RECIST 1.1 will likely recommend a reduction in the current 10-mm definition of minimum measurable disease. The concept of “target lesion” is integral to RECIST; this concept, however, lacks relevance in mesothelioma with its spatially extensive presentation. Modified RECIST 1.1, therefore, will formalize the substitution of “measurement site” for “target lesion” and will define a logical approach to the selection of up to six pleural measurement sites that meet the minimum measurable disease threshold (with an appropriate accommodation for bilateral disease). Modified RECIST 1.1 will allow for the inclusion of longest diameter measurements from a specified number of *non-pleural* lesions to supplement the pleural tumor measurements. A set of descriptive labels for *non-measurable* pleural disease will be identified in modified RECIST 1.1, and the role of non-measurable disease in the classification of progressive disease will be outlined. Furthermore, the meaning of a “new lesion” in the context of progressive disease in mesothelioma will be explored.

This session at the IMIG meeting provided a forum for discussion of response for malignant pleural mesothelioma, with the goal of moving towards harmonization of criteria for mesothelioma with the current RECIST 1.1. Forthcoming modified RECIST 1.1 guidelines are

expected to resolve discrepancies and alleviate confusion that has developed with regard to image-based mesothelioma tumor response assessment.

9. Conclusion

The 2016 International Conference of iMig highlighted a number of important imaging studies in malignant pleural mesothelioma. Intraoperative optical imaging of mesothelioma has the potential to become an important tool for surgeons seeking to achieve a macroscopic complete resection. The utility of MRI in mesothelioma continues to attract attention, from investigations of more advantageous contrast timing delays to the possible role of early contrast enhancement characteristics of pleural abnormalities in the detection of malignant tumors to the use of image features for patient survival stratification. Beyond MRI, contrast-enhancement in CT is being investigated to evaluate tumor hemodynamics as a potential indicator of tumor response separate from size-based metrics. Although tumor size derived from CT scans is expected to remain an important factor in patient management (with increased reliance on tumor volume), investigation continues to reveal only moderate correlation between CT-based tumor volume and physical tumor weight and volume. The 2016 iMig conference recognized the important role of imaging in the assessment of tumor response in clinical trials by entitling the imaging session “Imaging and Endpoint Evaluation;” this session thus provided an appropriate forum for discussion of the issues that motivate the newly announced effort to craft “modified RECIST 1.1” for mesothelioma. The biennial International Conference of iMig continues to provide an important opportunity to highlight imaging advances in the mesothelioma setting. The topics presented at the 2016 meeting are the focus of continued research effort and clinical investigation; further advances in these and other promising aspects of imaging are expected to be presented at iMig 2018 in Ottawa, Ontario, Canada.

Acknowledgments

The authors gratefully acknowledge the International Mesothelioma Interest Group (iMig) and all those who contributed to the 13th International Conference in Birmingham, United Kingdom, chaired by Dean Fennell, Ph.D., MRCP and David Waller, M.D.

JJK would like to thank Jarrod D. Predina, M.D., Sarah Nims, Ollin Venegas, John C. Kucharczuk, M.D., Charuhas Deshpande, M.D., Ryan Zeh, Sunil Singhal, M.D. The study of JJK was supported by National Institutes of Health R01 CA193556.

SK would like to thank Akash Patel, M.D., Ian Berger, B.S., E. Paul Wileyto, Ph.D., Urooj Khalid, Drew A. Torigian, M.D., and Arun Nachiappan, M.D.

ST would like to thank C.A. Humphreys, D.B. Stobo, G.W. Cowell, R. Woodward, J.E. Foster, C. Dick, and Kevin G. Blyth, MBChB, FRCP, M.D.

JC acknowledges F. De Keyzer, P. Naftoux, W. De Wever, E. Verbeken, J. Vansteenkiste, K. Nackaerts, and J. Verschakelen. The mesothelioma study of JC was supported by a grant (#ARC210) from the Belgian Foundation against Cancer.

EG would like to thank Samuel G. Armato III, Ph.D., Zacariah E. Labby, Ph.D., Christopher Straus, M.D., Feng Li, M.D., Ph.D., Buerkley Rose, R.N., and Hedy L. Kindler, M.D. EG was funded in part by the Kazan Law Firm's Charitable Foundation and the Paul C. Hodges Alumni Society, Department of Radiology, The University of Chicago.

IO would like to thank M. Friess, D.L. Nguyen-Kim, T. Frauenfelder, S. Hillinger, B. Seifert, I. Inci, and Walter Weder, M.D.

SGA receives royalties and licensing fees through The University of Chicago for computer-aided diagnosis technology. SGA is a consultant for Aduro Biotech, Inc.

AKN acknowledges the National Health and Medical Research Council of Australia for funding the National Centre for Asbestos Related Diseases Centre of Research Excellence.

KGB is funded by a National Research Scotland Career Research Fellowship.

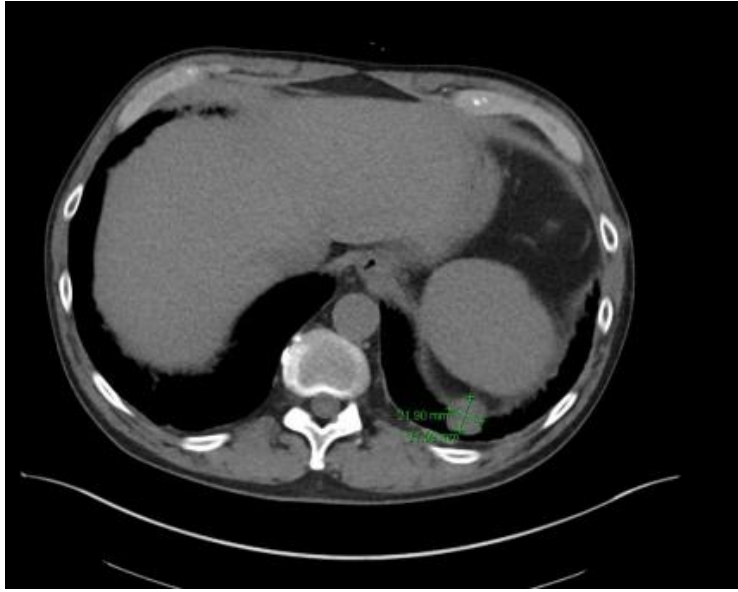
References

1. Armato SG III, Entwisle J, Truong MT, Nowak AK, Ceresoli GL, Zhao B, Misri R, Kindler HL. Current state and future directions of pleural mesothelioma imaging. *Lung Cancer* 2008;59:411–420.
2. Nowak AK, Armato SG III, Yildirim H, Ceresoli GL, Francis RJ. Imaging in pleural mesothelioma: A review of imaging research presented at the 9th International Meeting of the International Mesothelioma Interest Group. *Lung Cancer* 2010;70:1–6.
3. Armato SG III, Labby ZE, Coolen J, Klabatsa A, Feigen M, Persigehl T, Gill RR. Imaging in pleural mesothelioma: A review of the 11th International Conference of the International Mesothelioma Interest Group. *Lung Cancer* 2013;82:190–196.
4. Armato SG III, Coolen J, Nowak AK, Robinson C, Gill RR, Straus C, Khanwalkar A. Imaging in pleural mesothelioma: A review of the 12th International Conference of the International Mesothelioma Interest Group. *Lung Cancer* 2015;90:148–154.
5. Ntziachristos V, Ripoll J, Wang LV, Weissleder R. Looking and listening to light: The evolution of whole-body photonic imaging. *Nature Biotechnology* 2005;23:313–320.
6. Gill RR, Richards WG, Yeap BY, Matsuoka S, Wolf AS, Gerbaudo VH, Bueno R, Sugarbaker DJ, Hatabu H. Epithelial malignant pleural mesothelioma after extrapleural pneumonectomy: stratification of survival with CT-derived tumor volume. *AJR. American Journal of Roentgenology* 2012;198:359–63.
7. Labby ZE, Nowak AK, Dignam JJ, Straus C, Kindler HL, Armato SG III. Disease volumes as a marker for patient response in malignant pleural mesothelioma. *Annals of Oncology* 2013;24:999–1005.
8. Labby ZE, Armato SG III, Dignam JJ, Straus C, Kindler HL, Nowak AK. Lung volume measurements as a surrogate marker for patient response in malignant pleural mesothelioma. *Journal of Thoracic Oncology* 2013;8:478–486.
9. Liu F, Zhao B, Krug LM, Ishill NM, Lim RC, Guo P, Gorski M, Flores R, Moskowitz CS, Rusch VW, Schwartz LH. Assessment of therapy responses and prediction of survival in malignant pleural mesothelioma through computer-aided volumetric measurement on computed tomography scans. *Journal of Thoracic Oncology* 2010;5:879–84.
10. Frauenfelder T, Tutic M, Weder W, Gotti RP, Stahel RA, Seifert B, Opitz I. Volumetry: An alternative to assess therapy response for malignant pleural mesothelioma? *The European Respiratory Journal* 2011;38:162–8.
11. Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. *Journal of Thoracic & Cardiovascular Surgery* 1998;115:310–7.
12. Sensakovic WF, Armato SG, 3rd, Straus C, Roberts RY, Caligiuri P, Starkey A, Kindler HL. Computerized segmentation and measurement of malignant pleural mesothelioma. *Medical Physics* 2011;38:238–44.
13. Kircheva DY, Husain AN, Watson S, Kindler HL, Durkin A, Vigneswaran WT. *European Journal of Cardiothoracic Surgery*. 2016;49:1642–1647.

14. Armato SG III, Li P, Husain AN, Straus C, Khanwalkar A, Kindler HL, Vigneswaran WT. Radiologic-pathologic correlation of mesothelioma tumor volume. *Lung Cancer* 2015;87:278–282.
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, van Glabbeke M, van Oosteron AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. *Journal of the National Cancer Institute* 2000;92:205–16.
16. Miller AB, Hogestraeten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
17. Hillerdal G. Staging and evaluating responses in malignant pleural mesothelioma. *Lung Cancer*. 2004;43:75-6.
18. van Klaveren RJ, Aerts JG, de Bruin H, Giaccone G, Manegold C, van Meerbeeck JP. Inadequacy of the RECIST criteria for response evaluation in patients with malignant pleural mesothelioma. *Lung Cancer*. 2004;43:63-9.
19. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Annals of Oncology* 2004;15:257–60.
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer*. 2009;45:228-47.
21. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, Pass H, Asamura H, Waller D, Edwards J, Weder W, Hoffmann H, van Meerbeeck JP, IASLC Staging Committee. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *Journal of Thoracic Oncology*. 2012;7:1631-9.
22. Butchart EG, Ashcroft T, Barnsley WC, Holden MP. Pleuropneumectomy in the management of diffuse malignant mesothelioma of the pleura. Experience with 29 patients. *Thorax*. 1976;31:15-24.
23. Keating J, Tchou J, Okusanya O, Fisher C, Batiste R, Jiang J, Kennedy G, Nie S, Singhal S. Identification of breast cancer margins using intraoperative near-infrared imaging. *Journal of Surgical Oncology*. 2016;113:508-14.
24. Keating JJ, Kennedy GT, Singhal S. Identification of a subcentimeter pulmonary adenocarcinoma using intraoperative near-infrared imaging during video-assisted thoracoscopic surgery. *Journal of Thoracic and Cardiovascular Surgery*. 2015;149:e51-3.
25. Keating JJ, Okusanya OT, De Jesus E, Judy R, Jiang J, Deshpande C, Nie S, Low P, Singhal S. Intraoperative near-infrared fluorescence imaging and spectroscopy identifies residual tumor cells in wounds. *Molecular Imaging and Biology*. 2016;18:209-18.
26. Keating JJ, Nims S1, Venegas O, Jiang J, Holt D, Kucharczuk JC, Deshpande C, Singhal S. Intraoperative imaging identifies thymoma margins following neoadjuvant chemotherapy. *Oncotarget*. 2016;7:3059-67.

27. Heelan RT, Rusch VW, Begg CB, Panicek DM, Caravelli JF, Eisen C. Staging of malignant pleural mesothelioma: comparison of CT and MR imaging. *AJR American Journal of Roentgenology*. 1999;172:1039-47.
28. Corson N, Sensakovic WF, Straus C, Starkey A, Armato SG III. Characterization of mesothelioma and tissues present in contrast-enhanced thoracic CT scans. *Medical Physics*. 2011;38:942–947.
29. Hallifax RJ, Haris M, Corcoran JP, Leyakathalikhhan S, Brown E, Srikantharaja D, et al. Role of CT in assessing pleural malignancy prior to thoracoscopy. *Thorax*. 2015;70:192–193.
30. Tsim S, Blyth KG. *American Journal of Respiratory and Critical Care Medicine*. 2016;193:A6392.
31. Kumar-Singh S, Weyler J, Martin MJ, Vermeulen PB, Van Marck E. Angiogenic cytokines in mesothelioma: a study of VEGF, FGF-1 and -2, and TGF beta expression. *Journal of Pathology*. 1999;189:72–78.
32. Maeda J, Ueki N, Ohkawa T, Iwahashi N, Nakano T, Hada T, et al. Transforming growth factor-beta 1 (TGF-beta 1)- and beta 2-like activities in malignant pleural effusions caused by malignant mesothelioma or primary lung cancer. *Clinical Experience in Immunology*. 1994;98:319–322.
33. Kang H, Lee HY, Lee KS and Kim J-H. Imaging-based tumor treatment response evaluation: Review of conventional, new, and emerging concepts. *Korean Journal of Radiology*. 2012;13:371-90.
34. Hagemann P, Jonasson L, Maeder P, Thiran JP, Wedeen VJ, Meuli R. Understanding diffusion MR imaging techniques: From scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. *Radiographics*. 2006;26:S205-223.
35. Coolen J, De Keyser F, Naftoux P, De Wever W, Doooms C, Vansteenkiste J, Roebben I, Verbeken E, De Leyn P, Van Raemdonck D, Nackaerts K, Dymarkowski S, Verschakelen J. Malignant pleural disease: Diagnosis by using diffusion-weighted and dynamic contrast-enhanced MR imaging--initial experience. *Radiology*. 2012;263:884-92.
36. Cheng L, Tunariu N, Collins DJ, Blackledge MD, Riddell AM, Leach MO, Popat S, Koh DM. Response evaluation in mesothelioma: Beyond RECIST. *Lung Cancer*. 2015;90:433-41.
37. Choi MH, Oh SN, Rha SE, Choi J-I, Lee SH, Jang HS, Kim J-G, Grimm R, Son Y. Diffusion-weighted imaging: Apparent diffusion coefficient histogram analysis for detecting pathologic complete response to chemotherapy in locally advanced rectal cancer. *Journal of Magnetic Resonance Imaging*. 2015;Dec 15. [Epub ahead of print].
38. García-Figueiras R, Goh VJ, Padhani AR, Baleato-González S, Garrido M, León L, Gómez-Caamaño A. CT perfusion in oncologic imaging: A useful tool?, *AJR American Journal of Roentgenology*. 2013;200:8–19.

39. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage*. 2011;54:2033–2044.
40. Miles KA. Perfusion CT for the assessment of tumour vascularity: Which protocol? *British Journal of Radiology*. 2003;76:S36-42.
41. Miles KA, Griffiths MR. Perfusion CT: A worthwhile enhancement? *British Journal of Radiology*. 2003;76:220–31.
42. Opitz I, Friess M, Kestenholz P, Schneiter D, Frauenfelder T, Nguyen-Kim TD, Seifert B, Hoda MA, Klepetko W, Stahel RA, Weder W. A new prognostic score supporting treatment allocation for multimodality therapy for malignant pleural mesothelioma: A review of 12 years' experience. *Journal of Thoracic Oncology*. 2015;10:1634-41.
43. Tsao AS, Garland L, Redman M, Kernstine K, Gandara D, Marom EM. A practical guide of the Southwest Oncology Group to measure malignant pleural mesothelioma tumors by RECIST and modified RECIST criteria. *Journal of Thoracic Oncology*. 2011;6:1–4.
44. Armato SG III, Ogarek JL, Starkey A, Vogelzang NJ, Kindler HL, Kocherginsky M, MacMahon H. Variability in mesothelioma tumor response classification. *AJR American Journal of Roentgenology*. 2006;186:1000–1006.
45. Armato SG III, Oxnard GR, MacMahon H, Vogelzang NJ, Kindler HL, Kocherginsky M, Starkey A. Measurement of mesothelioma on thoracic CT scans: A comparison of manual and computer-assisted techniques. *Medical Physics*. 2004;31:1105–1115.
46. Oxnard GR, Armato SG III, Kindler HL. Modeling of mesothelioma growth demonstrates weaknesses of current response criteria. *Lung Cancer*. 2006;52:141–148.
47. Labby ZE, Armato SG III, Kindler HL, Dignam JJ, Hasani A, Nowak AK. Optimization of response classification criteria for patients with malignant mesothelioma. *Journal of Thoracic Oncology*. 2012;7:1728–1734.
48. Armato SG III, Nowak AK, Francis RJ, Kocherginsky M, Byrne MJ. Observer variability in mesothelioma tumor thickness measurements: Defining minimally measurable lesions. *Journal of Thoracic Oncology*. 2014;9:1187–1194.

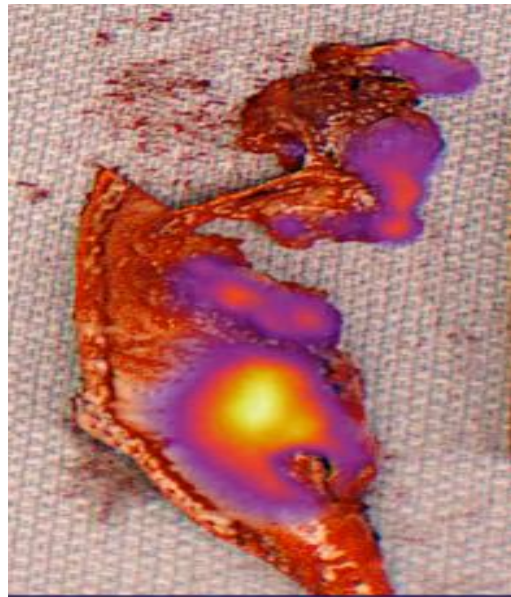


49.

(a)



(b)



(c)

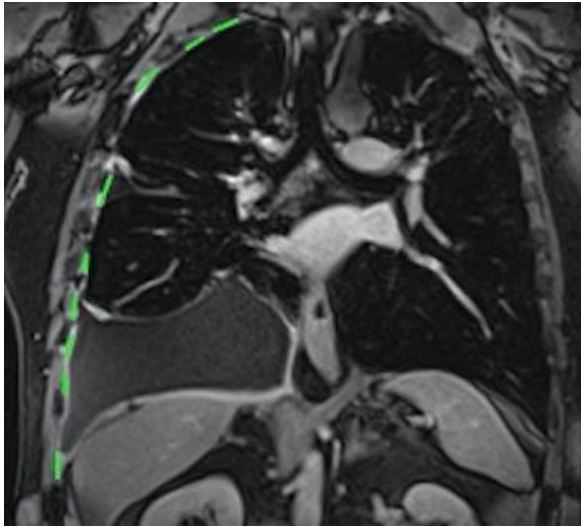
FIGURE 1. (a) Pre-operative CT scan demonstrating focus of left-sided tumor.

Resected tumor specimen imaged in (b) white light and (c) near infrared light (superimposed on the white-light image).

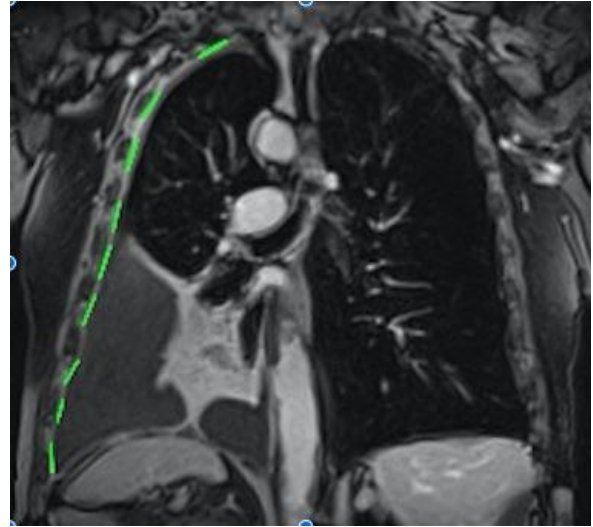
a.

b.

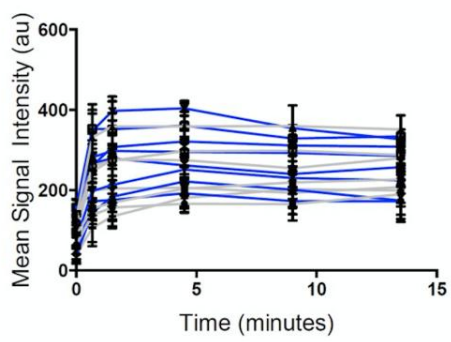
FIGURE 2. Delayed enhanced images demonstrate chest wall invasion. (a) Pre-contrast and (b) delayed contrast-enhanced fat-saturated T1-weighted images in a 54-year-old male with right-sided malignant pleural mesothelioma reveal robust differentiation of tumor (white arrow) from adjacent fluid with delayed phase enhancement.



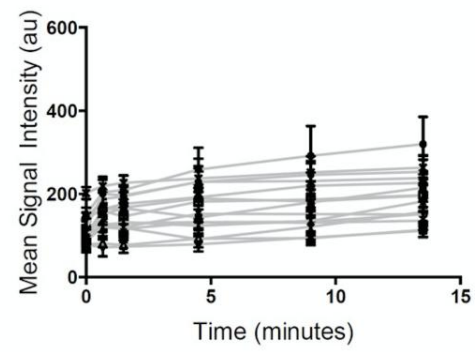
(a)



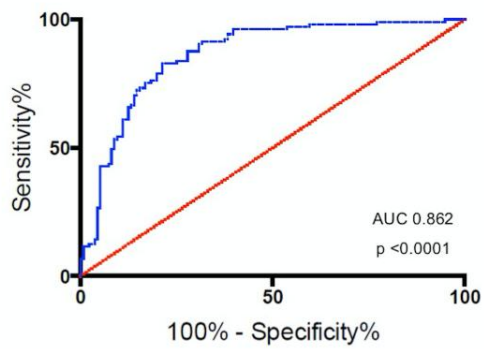
(b)



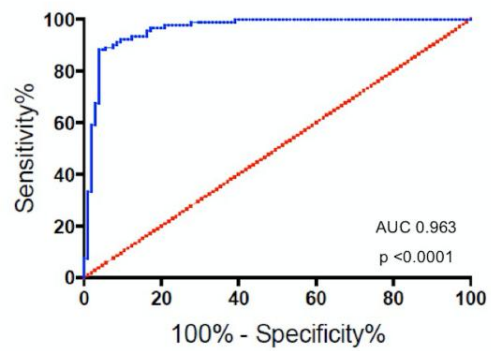
(c)



(d)



(e)



(f)

FIGURE 3. (a) and (b) T1-weighted images acquired 4.5 minutes after contrast injection, with ROIs show in green. (c) Signal intensity vs. time curve with 8 out of 15 ROIs demonstrating ECE (classified as malignant). (d) Signal intensity vs. time curve with no ROIs demonstrating ECE (classified as benign). (e) ROC curve based on signal-intensity gradient from all ROIs regardless of the presence or absence of ECE. (f) ROC curve based on signal-intensity gradient from ECE-positive ROIs only, demonstrating superior discriminatory performance.

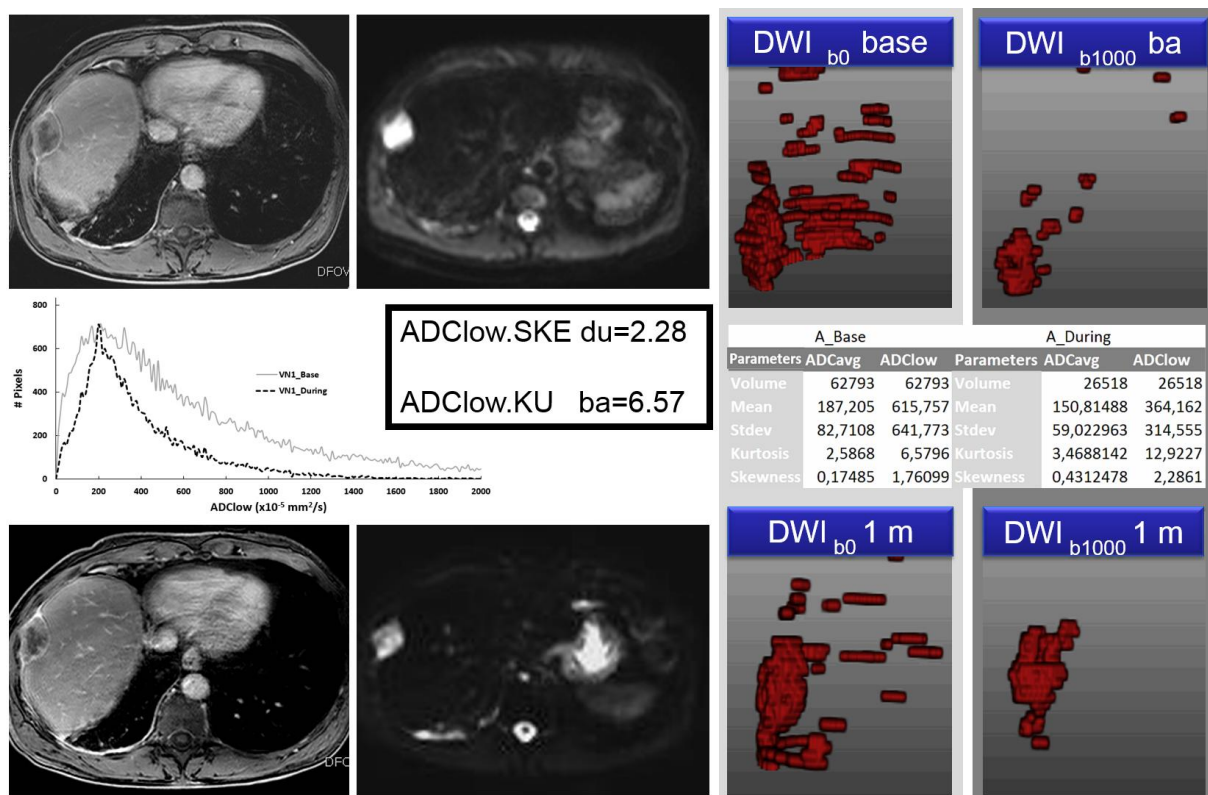


FIGURE 4. 45-year-old male with mesothelioma in the right hemithorax and chest wall and diaphragmatic invasion (OS: 650 days) scanned before and during systemic palliative chemotherapy. Post-contrast 3D T1-weighted and DWI images at baseline (top row) and 1 month before the second cycle of chemotherapy (bottom row) are shown along with 3D DWI volumetric data and fused b0/1000-ADC data on the left. The follow-up scan histogram (dotted line) has a more acute peak (higher kurtosis) with a slight shift to the left (more positive skewness).

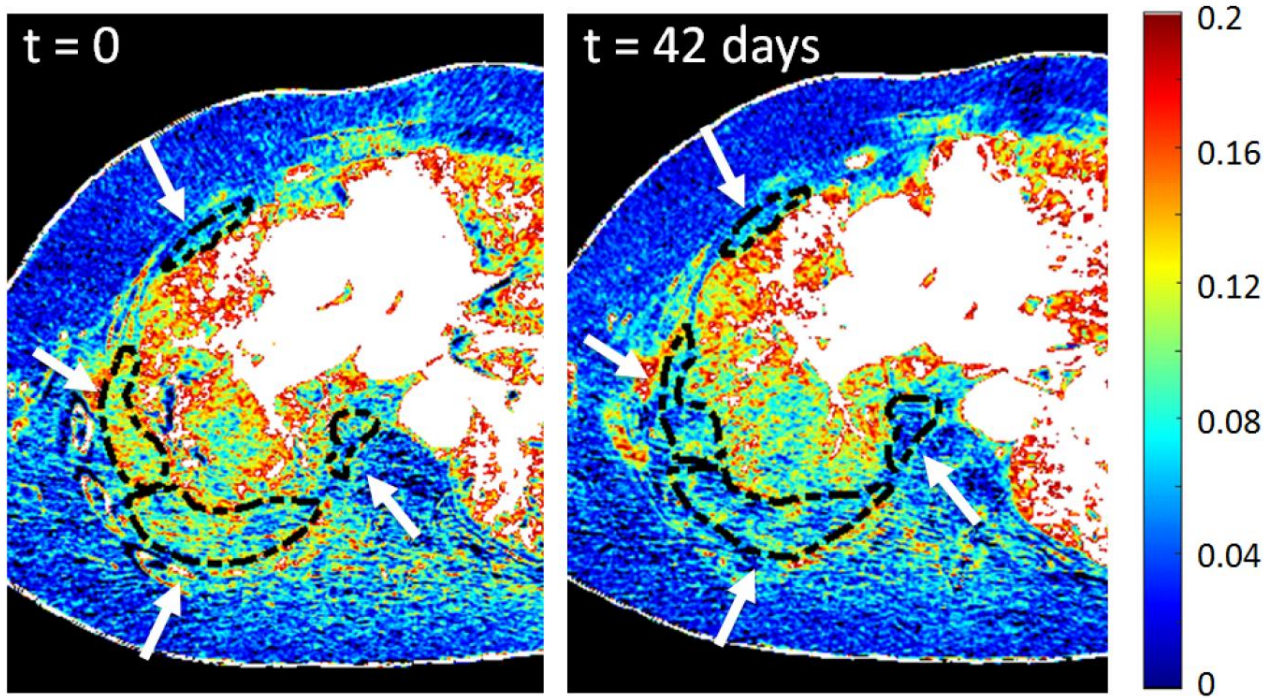


FIGURE 5. Blood volume parameter maps of a patient before (left) and after (right) two cycles of chemotherapy. Mesothelioma tumor contours (dashed lines) are indicated with arrows. The image values are unitless. The mean value of the blood volume parameter for the tumors shown was 0.072 in the first scan and 0.054 in the second scan (a relative decrease of 25.6% between scans), whereas modified-RECIST-based tumor thickness measurements increased by 12.8%.

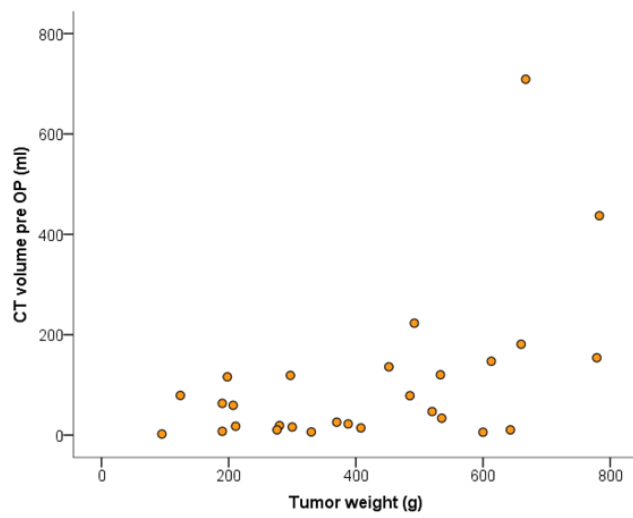


FIGURE 6. CT-based tumor volume plotted as a function of post-surgical tumor weight.

Spearman rank correlation coefficient 0.47, $p=0.01$.

Modified RECIST Gaps in Application

1. Definition of minimum measurable disease was not stated (intended concordance with RECIST 1.0)
2. Not explicit about the need to permanently record an image of the site and vector of measurement.
3. Not explicit about the incorporation of measurement of lymph-adenopathy into response assessment.
4. Did not address the potential for early reporting of progression where response had reduced pleural thickening to a non-measurable level
5. Did not provide guidance for measurement and response in the setting of non-pleural lesions but no measurable pleural disease
6. Did not provide guidance on measurement of fissural pleural thickening
7. Did not provide guidance on measurement of bilateral pleural disease

FIGURE 7. Keys gaps in application, unaddressed or misinterpreted issues, and logistical concerns in the practical implementation of modified RECIST that have become apparent since its publication.